Prognostic value of positron emission tomography/computed tomography in transplant-eligible newly diagnosed multiple myeloma patients from CASSIOPEIA: the CASSIOPET study

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) is a reliable imaging technique for evaluating and monitoring multiple myeloma (MM) patients with a prognostic value for progression-free survival (PFS) and overall survival.[1-5] PET/CT-positive features at diagnosis have indeed been found to correlate with poorer outcomes.[3,6] Here, we report the first results of CASSIOPET, a companion study of CASSIOPEIA (*clinicaltrials gov. Identifier: NCT02541383*),[7,8] which evaluated the prognostic value of baseline PET/CT on PFS. Study design and eligibility criteria for the CASSIOPEIA trial have been previously published.[7] Briefly, transplant-eligible patients with newly diagnosed MM (NDMM) were randomized 1:1 to receive four 28-day, pre-autologous stem cell transplant (ASCT) induction cycles and two 28-day post-ASCT consolidation treatment cycles of daratumumab plus bortezomib/thalidomide/dexamethasone (D-VTd) or bortezomib/thalidomide/dexamethasone (VTd) in CASSIOPEIA Part 1. The primary endpoint, stringent complete response, was evaluated 100 days after ASCT. In CASSIOPEIA Part 2, patients achieving a partial response (PR) or better 100 days post-ASCT underwent a second 1:1 randomization to observation or maintenance therapy with intravenous daratumumab 16 mg/kg every 8 weeks for up to 2 years.

Among patients randomized in CASSIOPEIA, those eligible for inclusion in CASSIOPET had received a PET/CT scan ≤6 weeks before randomization in CASSIOPEIA. Patients were excluded if they were unable to access or undergo PET/CT investigation, had uncontrolled diabetes, or had received steroids ≤12 hours before the PET/CT scan. All patients provided written informed consent.

The primary endpoint of the CASSIOPET study is PFS from the second CASSIOPEIA randomization. This PFS analysis for CASSIOPEIA was recently reported.[8] CASSIOPET analyses reported here evaluate the prognostic value of PET/CT at baseline on PFS from the first CASSIOPEIA randomization, PFS differences between baseline PET-negative *versus* PET-positive patients in each treatment arm, and the effect of daratumumab on PET/CT negativity at post-consolidation.

PET/CT scans were performed at baseline and post-consolidation (day 100 [±7 days] post-ASCT). All patients had fasted for ≥6 hours before the PET/CT scan. No dexamethasone was to be administered ≤12 hours before the PET/CT scan. Blood glucose levels were measured before ^{18}F-FDG injection with a preferred glycemia level ≤150 mg/dL. No insulin was administered ≤2 hours before ^{18}F-FDG injection, and no oral contrast was given. Whole-body imaging was performed 55 to 75 minutes after the ^{18}F-FDG injection. First scout and low-dose CT data (head to feet) were obtained, followed by PET data acquisition, image reconstruction, and analysis.

Acquired imaging data were uploaded to a central electronic repository system (KEOSYS, Saint-Herblain, France) and analyzed using the IMAGYS platform. Five-point Deauville scores (range, 1-5)[9] were applied to bone marrow (BM), bone focal lesions (FL), extramedullary disease (EMD), and paramedullary disease (PMD). Localization of the most intense ^{18}F-FDG uptake was identified, and the maximal standardized uptake value (SUV_{max}) was calculated. Bone SUV_{max} was defined as the hottest value between BM, FL, and PMD. PET images were interpreted (blinded to patient treatment) by an independent team of nuclear-medicine physicians with extensive MM experience. PET/CT scan assessments did not include separate assessments of CT scans; thus, patients may have been PET-negative but could still display lytic lesions in the CT scan.

PET–complete response (PET-CR) was defined as an uptake of less than or equal to the mediastinal blood pool in all localizations. PET–unconfirmed CR (PET-uCR) was defined as an uptake between the mediastinal blood pool and liver. PET-PR was defined as a decrease in the number and/or activity of BM, FL, EMD, or PMD but persistence of lesions with uptake above liver activity or BM uptake above liver activity. Patients with PET–stable disease (PET-SD) had no significant modification of FL, EMD, or PMD compared with baseline. Patients with PET–progressive disease (PET-PD) had a new lesion (FL, EMD, or PMD) compared with baseline. PET/CT-positive patients were defined as patients with PET-PR and PET-SD. PET/CT-negative patients were defined as patients with PET-CR and PET-uCR. Clinical response was assessed according to International Myeloma Working Group criteria.[10]

The prognostic effect of including explanatory PET/CT variables on PFS was assessed using Cox regression models. Seven baseline PET/CT characteristics were

chosen based on expert knowledge: PET positivity, presence of FL, BM infiltration, PMD, EMD, FL SUV_{max}, and bone SUV_{max}.

The prognostic effect of each of the seven baseline PET characteristics was estimated using a univariable Cox model in addition to the prognostic effect of known prognostic factors: serum lactate dehydrogenase (LDH) levels, serum β_2 microglobulin concentration, cytogenetic risk, and International Staging System (ISS) disease staging.

The prognostic effect of each of the seven baseline PET characteristics was then estimated adjusting for the treatment group and revised ISS (r-ISS). These covariates were chosen based on expert knowledge without statistical covariate selection procedures due to the relatively small number of PFS events. Adjustment for treatment group accounts for the randomized design of CASSIOPEIA, of which CASSIOPET is an ancillary study. r-ISS is the current stratification score for myeloma patients and combines ISS (which includes serum β_2 microglobulin and serum albumin), cytogenetic risk, and serum LDH level into a single variable.

A final multivariable Cox model was constructed including the seven baseline PET characteristics and adjusting for treatment and r-ISS. At the time of analysis, 20 PFS events were observed in the D-VTd group and 34 in the VTd group. Thus, the third multivariable Cox model results are exploratory and should be interpreted cautiously due to the low ratio of events per variable.

Proportional hazards and log-linearity of effects were assessed. No statistically significant violations of the proportional hazard assumption were detected at the customary 5% *P* value threshold using the Schoenfeld residuals. No violation of the log-linearity assumption was detected using *P* splines. The presence of multicollinearity was assessed using the variance inflation factor; no value exceeded 2 for all PET/CT characteristics.

The log-rank estimator with Kaplan–Meier representation was used to describe PFS. Baseline and post-consolidation PET/CT negativity rates were compared between treatment groups using the chi-square test, odds ratios, and 2-sided 95% confidence intervals (CI). The role of interactions between baseline PET positivity and treatment in the PFS distribution could not be assessed, as zero PFS events were observed in the D-VTd PET-negative group, leading to a hazard ratio (HR) of 0 with a non-estimable variance using classical statistical tests.

The primary results of CASSIOPEIA Part 1 have been reported (median follow-up, 18.8 months).[7] The current analysis of CASSIOPET was performed using patient data with a median follow-up time of 29.2 months. Of 1,085 patients enrolled in CASSIOPEIA, 268 (D-VTd, n=137; VTd, n=131) had assessable baseline PET; 184 (D-VTd, n=101; VTd, n=83) patients were also PET-evaluable post-consolidation (Figure 1). Baseline characteristics of patients with assessable baseline PET were similar to those in the overall CASSIOPEIA trial (*Online Supplementary Table S1*). At baseline, 54 patients (20%) were PET-negative and 214 (80%) were PET-positive.

PFS was better for baseline PET-negative *versus* PET-positive patients (hazard ratio [HR]: 0.42, 95% CI: 0.18-0.97,

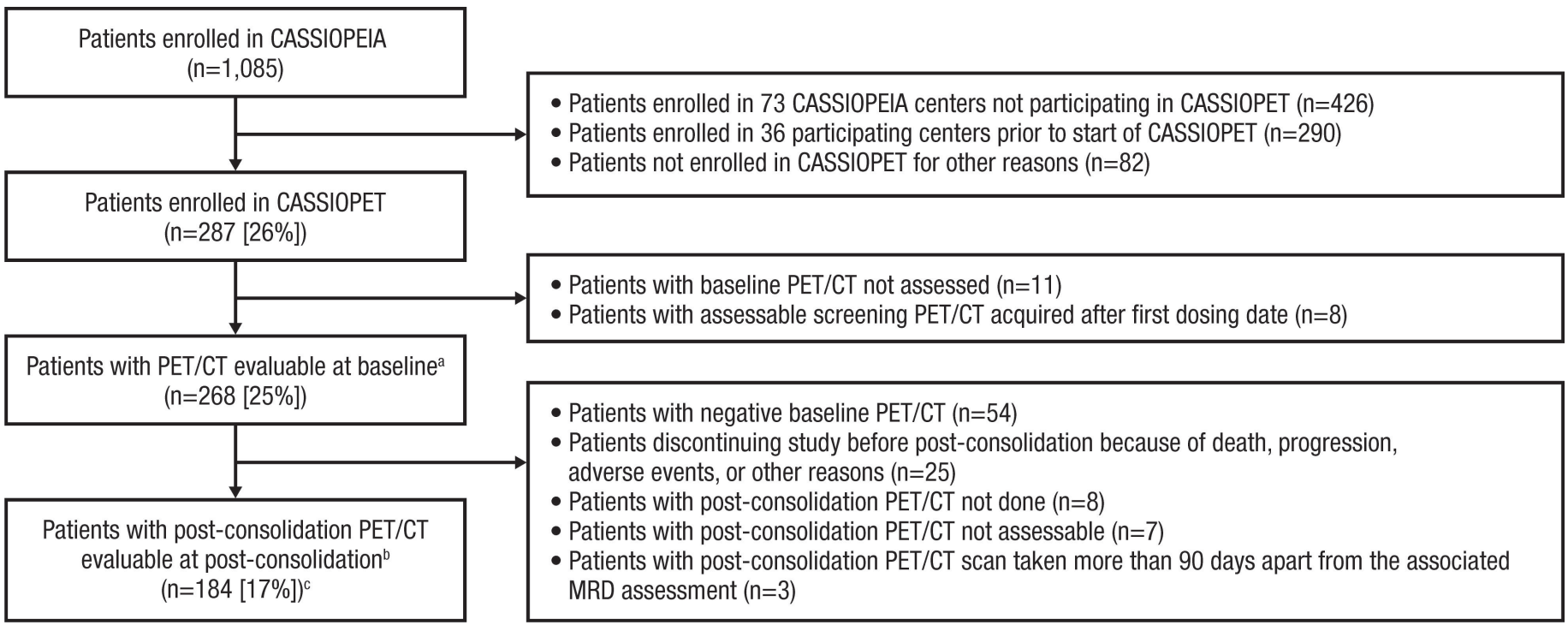

Figure 1. STROBE flow chart for CASSIOPET. ASCT: autologous stem cell transplant; MRD: minimal residual disease; PET: positron emission tomography; PET/CT: positron emission tomography/computed tomography. [a]Baseline PET–evaluable patients were defined as patients with assessable baseline PET acquired before the first dosing date. [b]Post-consolidation PET–evaluable patients included patients with assessable day 100 post-ASCT PET data and positive baseline PET but excluded patients with a date of PET/CT post-consolidation >±90 days from the date of the day 100 MRD assessment. [c]13 patients had unevaluable baseline PET/CT but evaluable post-consolidation PET/CT and were included in the post-consolidation analysis.

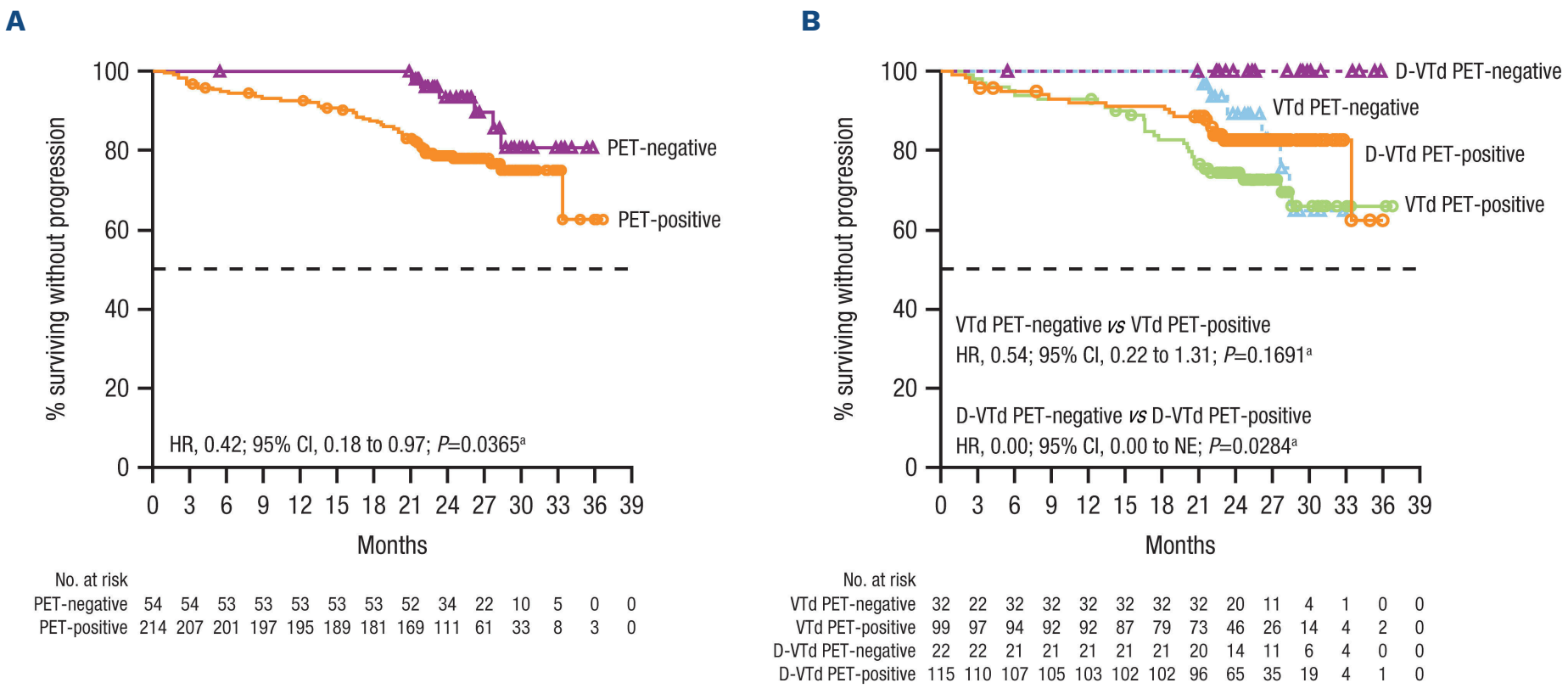

Figure 2. Progression-free survival outcomes by baseline positron emission tomography/computed tomography status in CASSIOPET. (A) Progression-free survival (PFS) for baseline positron emission tomography (PET)-negative patients *versus* PET-positive patients and (B) PFS for baseline PET-negative patients *versus* PET-positive patients by treatment group. Baseline PET assessments were performed prior to the first dose of study drug, and PFS was based on time from first randomization. CI: confidence interval; D-VTd: daratumumab plus bortezomib/thalidomide/dexamethasone; HR: hazard ratio; NE: not estimable; VTd: bortezomib/thalidomide/dexamethasone. [a]Based on a log-rank test.

P=0.0365; Figure 2A). The 12- and 18-month PFS rates were higher in patients who were PET-negative (12- and 18-month rates, 100%) *versus* PET-positive (12-month rate, 93%; 18-month rate, 87%) at baseline. When stratified by treatment group, PFS was better among patients who were PET-negative *versus* PET-positive in the D-VTd arm. However, PFS was not significantly different in the VTd arm (Figure 2B). By univariable analysis, baseline PET characteristics associated with PFS were PMD (*P*<0.001), EMD (*P*=0.034), FL (*P*=0.047), FL SUV_{max} (*P*=0.043), and bone SUV_{max} (*P*=0.021). All these characteristics, except for FL, remained prognostic factors when adjusting for treatment arm and r-ISS (Table 1). A multivariable analysis including all PET/CT characteristics and adjusting for treatment arm and r-ISS showed that PMD (HR: 3.16, 95% CI: 1.60-6.28) and EMD (HR: 2.32, 95% CI: 1.04-5.19) remained independently associated with a higher risk of relapse or death (Table 1).

Of the 184 patients with post-consolidation PET measurements, 118 (64%) were assessed as PET-CR and 47 (26%) as PET-uCR (*Online Supplementary Table S2*). Seventeen (9%) patients were assessed as PET-PR and two (1%) as PET-SD. Overall, 165 (90%) patients were PET-negative and 19 (10%) were PET-positive. The rates of PET negativity were high and similar between the D-VTd (90%) and VTd (89%) groups.

Results of the CASSIOPET study presented here confirm that baseline PET/CT findings have a prognostic value for PFS. PFS was indeed better for baseline PET-negative *versus* PET-positive NDMM patients, including patients treated with daratumumab. The presence of PMD, EMD, FL, and the FL SUV_{max} and bone SUV_{max} were associated with shorter PFS. When adjusting for treatment arm and classical NDMM (r-ISS) prognostic score, PMD and EMD had independent prognostic value. PET-CR post-consolidation rates were high and similar in both D-VTd and VTd groups.

PET/CT is negative in approximately 10-20% of symptomatic MM patients. This study shows that PET/CT negativity, even if considered as false-negative for disease detection, could be considered for its prognostic value. Rasche *et al.* demonstrated that ^{18}F-FDG PET/CT may be considered ineffective for approximately 11% of patients due to low expression of the hexokinase 2 enzyme.[11] However, another study of 90 NDMM patients receiving novel agents during induction therapy showed that low hexokinase 2 expression associated with PET/CT negativity correlated with relatively better prognosis *versus* PET/CT-positive patients.[4] Baseline PET/CT-negative patients may thus represent a less aggressive subgroup of MM patients, associated with better outcomes in the setting of quadruplet therapy and ASCT.

This prospective study demonstrates PMD as an independent prognostic factor in MM. Previous prospective studies have shown the prognostic value of EMD, SUV_{max}, and FL number.[2,5,6,12,13] However, these studies neither described nor assessed PMD as a potential prognostic biomarker. In the prospective IMAJEM study that

demonstrated the prognostic value of EMD, EMD was detected at a similar percentage (7.5%) as in CASSIOPET (5-11%), but PMD was considered as FL.[2] The independent prognostic value of PMD shown here is consistent with data from Rasche *et al.*, indicating the presence of large focal lesions as a strong independent poor prognosis factor in NDMM.[14,15]

Spatial heterogeneity can limit the sensitivity of risk classification based on cytogenetics and gene expression profiling because these tests are based on cells obtained from a single BM biopsy. Rasche *et al*. have shown that high-risk genomic alterations can be present in focal lesions, yet absent in other locations.[14] Combined with the results of other studies,[2,5] several PET/CT characteristics could be defined as possible high-risk biomarkers and used to define high-risk patients at the initial diagnosis of symptomatic MM.

The IMAJEM study[2] used background liver uptake to define

Table 1. Univariable and multivariable analyses of the prognostic value of baseline positron emission tomography (PET) characteristics on progression-free survival based on all patients with PET measurements at baseline (54/268 progression-free survival events).

Baseline characteristics	PFS events (n/N)	Univariable analysis		Analysis adjusted for treatment group and r-ISS		Multivariable analysis adjusted for treatment group, r-ISS, and all baseline PET/CT characteristics	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PET status							
Positive	48/214	1.00	0.037	1.00	0.039	1.00	0.372
Negative	6/54	0.42 (0.18-0.97)		0.41 (0.17-0.95)		0.55 (0.15-2.04)	
Presence of FL							
No	12/88	1.00	0.047	1.00	0.051	1.00	0.753
Yes	42/180	1.90 (1.00-3.60)		1.90 (1.00-3.62)		0.84 (0.29-2.44)	
Presence of diffuse BM infiltration[a]			0.220		0.234		0.922
No	24/139	1.00		1.00		1.00	
Yes	30/129	1.40 (0.82-2.39)		1.39 (0.81-2.39)		1.03 (0.54-1.96)	
Presence of PMD			<0.001		<0.0001		0.001
No	36/221	1.00		1.00		1.00	
Yes	18/47	2.81 (1.59-4.98)		3.82 (2.11-6.92)		3.16 (1.60-6.28)	
Presence of EMD			0.034		0.012		0.041
No	46/247	1.00		1.00		1.00	
Yes	8/21	2.21 (1.04-4.69)		2.68 (1.24-5.77)		2.32 (1.04-5.19)	
FL hottest SUV_{max}[b,c]		1.03 (1.00-1.06)	0.043	1.06 (1.02-1.10)	0.002	0.96 (0.85-1.08)	0.479
Bone SUV_{max}[c]		1.04 (1.01-1.07)	0.021	1.06 (1.03-1.10)	<0.001	1.07 (0.96-1.19)	0.223
LDH							
<Upper limit	24/155	1.00	0.017	—[d]	—	—	—
≥Upper limit	28/103	1.92 (1.11-3.31)		—[d]		—	
Cytogenetic risk							
Standard	41/219	1.00	0.158	—[d]	—	—	—
High	13/49	1.56 (0.84-2.92)		—[d]		—	
Serum β_2 microglobulin							
<3.5 mg/L	27/167	1.00	0.009	—[d]	—	—	—
3.5-5.4 mg/L	13/62	1.43 (0.74-2.78)		—[d]		—	
>5.4 mg/L	14/39	2.68 (1.40-5.12)		—[d]		—	
ISS stage							
I	18/118	1.00	0.010	—	—	—	—
II	22/111	1.34 (0.72-2.50)		—[d]		—	
III	14/39	2.80 (1.39-5.65)		—[d]		—	

BM: bone marrow; CI: confidence interval; EMD: extramedullary disease; FL: focal lesion; HR: hazard ratio; ISS: IMWG International Staging System; IMWG: International Myeloma Working Group; LDH: lactate dehydrogenase; PET: positron emission tomography; PFS: progression-free survival; PMD: paramedullary disease; r-ISS: IMWG revised International Staging System; SUV_{max}: maximum standardized uptake value. [a]Diffuse BM infiltration is considered to be present if visual analysis (Deauville scale) of BM uptake indicates the residual uptake to be > liver activity (4) or >> liver activity (5); otherwise, the diffuse BM infiltration is considered to be absent. [b]Imputed to 1 for patients with no presence of FL. [c]Highest result among FL hottest SUV_{max}, BM uptake SUV_{max}, PMD hottest SUV_{max}. Imputed FL hottest SUV_{max} to 1 for patients with no presence of FL. [d]Covariates not included in the adjusted analysis.

PET/CT negativity, similar to the CASSIOPET study, and was recommended in the recent standardization by Zamagni *et al.*[5] Regardless of the differing efficacies and regimens, both studies support the prognostic value of PET/CT.

In conclusion, baseline PET/CT findings appear to have a prognostic value for PFS. Longer follow-up in CASSIOPEIA Part 2 will provide additional insight.

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Contributions

All authors contributed to the study design, study execution, data analysis, and manuscript writing. All authors provided a full review of the manuscript and are fully responsible for all content and editorial decisions, were involved in all stages of manuscript development, and have approved the final version.

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Data-sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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